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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,805	01/21/2005	Katja Wosikowski-Buters	2923-686	3802

6449 7590 10/21/2008

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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,805	WOSIKOWSKI-BUTERS ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-49,53-56 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-49, 53-56 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 7-17-08 is acknowledged.

Claims included in the prosecution are 28-49, 53-56 and 58.

Claim Rejections - 35 USC § 112

1. Claims 28-49, 53-56 and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for N~-(2,4,6-triisopropylphenylsulfonyl)-3-amidino-(L)-phenylalanine 4-ethoxycarbonylpiperazide (WX-UKI) encapsulated in liposomes containing PC and PG in specific ratios and hemolysis as the side effect, does not reasonably provide enablement for generic liposomes and multitudes of compounds fitting in the generic 'amidino and guanidine derivatives of phenylalanine of the general formula claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

1) The nature of the invention: the invention concerns with pharmaceutical liposomal compositions containing 3 amidino or 3 guanidino phenylalanine derivatives of general formula with reduced unwanted side effects.

2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal sustained release compositions.

3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

4) The predictability or unpredictability in the art: Instant specification does not teach if the compounds are available or have to be made and what specific side effects these compounds have or the severity of the side effects when administered. The only statement is on page 4 lines 6-14 of the specification citing the PCT and DE applications which disclose the urokinase inhibitors. According to applicant's own arguments on page 15 of the response regarding Ben-Hur cited by the examiner the side-effect reducing capacity of the liposomes depend upon the nature of the liposomal components. If such were the case, one cannot extrapolate the results obtained from a single active agent WX-UKI using a specific liposomal composition to predict the effectiveness to multitudes of the urokinase inhibitors claimed encapsulated in any other liposomal composition.

5). the breadth of the claims: instant claim is very broad in terms of the active agents and term 'liposomes' which include unilamellar, multilamellar, paucilamellar and multivesicular liposomes and the lipids making up these liposomes.

6) The amount of direction of guidance provided: instant specification provides guidance to encapsulation of an amidino compound in liposomes made of PC and PG in a specific ratio and its effects on hemolysis. No other side effects are studied.

7) The presence or absence of working examples: as pointed out above, what is provided in the specification is a method of making the formulation containing WX-UKI and its effect on hemolysis and nothing else.

8) The quantity of experimentation necessary: it would require undue experimentation to determine what the side effects of the multitudes of the compounds are and their severity and determine which of the phospholipid(s) making up the liposomes reduce those side effects.

Applicant's arguments have been fully considered, but are not persuasive. Applicant in response states that to overcome the rejection, claim 28 has been amended and is presently limited to a formulation encapsulated within a phospholipidic liposome that reduces at least one side-effect selected from the group consisting of hemolysis and skin irritation. The rejection is maintained since this amendment is not fully responsive to the issues raised. Since liposomes are generally made of phospholipids, amending the claims to recite 'phospholipidic liposomes' is not fully responsive.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 28-49, 53-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723) or DE 102 25 876.7 cited on page 4 of the specification by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck (4,186,183) by themselves or in combination.

WO 00 teaches the claimed compounds (Examples in English equivalent). WO further suggests that these compounds can be incorporated into the membranes of liposomes and facilitate the targeting of cytotoxic agents such as doxorubicin (0069 of English equivalent). What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids. Since the amounts of the active agent depend upon the condition of the patient and the nature of the disease, it would have been obvious to one of ordinary skill in the art to vary the amounts in order to obtain the best possible results. The use of phospholipids as the liposome forming material would have been obvious to one ordinary skill in the art since phospholipids are routinely used for the formation of liposomes.

DE cited in the specification discloses instant 3 guanidine-phenylalanine derivatives as urokinase inhibitors. DE however, does not appear to teach liposomal formulations.

Caster teaches that liposomes are used as carriers for drug and they can be made with different features which can enhance a drug's efficacy, reduce the drug's toxicity and prolong the therapeutic effect (col. 1, lines 32-36 and examples).

Poiani teaches that drug toxicity could be reduced by selective drug delivery to the effected site using liposomes (col. 11, lines12-22).

Steck while disclosing a treatment for leishmaniasis teaches that liposome encapsulated drugs would have decreased liability for producing toxic side-effects (col. 2, lines 23-33).

The use of liposomes for the delivery of claimed urokinase inhibitors would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since WO and DE teach that these compounds are known urokinase inhibitors and WO in particular is suggestive of the use of the liposomes. One of ordinary skill in the art would be motivated further to use liposomes as carriers since the references of Caster, Poiani and Steck teach liposomes reduce the toxic effects of drugs.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that none of the cited references or combination of these references renders the present claims obvious without hindsight. Applicant further argues that the present inventors have discovered very specific formulations for obtaining the desired effects of the active ingredients while, at the same time, reducing unwanted side effects. According to applicant, claim 28 has been amended to reflect the specific limitations of this formulation by reducing the specific effective concentration range of the active ingredient in a formulation comprising phospholipidic liposomes. These arguments are

not persuasive since the references clearly teach the claimed compounds as anti-tumor agents and the amounts of the active agent used depends upon the type of tumor, severity of the disease and other factors and the secondary references clearly teach the effectiveness of liposomes in drug delivery and the ability of the liposomes to reduce the toxicity of the drugs. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant's arguments that the administration of the liposomal formulation required by present claim 28 surprisingly leads to prevention of undesirable side effects such as hemolysis and US 2003 is silent with respect to the side effects are not persuasive. That liposomes reduce the hemolysis of active agents is well -known in the art. The examiner has already cited the references of Ben-Hur, 6,010,890 (col. 6, lines 63-65); Kurono, 4,906,477 (col. 4, lines 10-13) in this context. Therefore, what is observed by applicant is to be expected and not an unexpected finding.

4. Claims 28-32 and 41-48, 53-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 28-37, 41-48 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US

2003/0013723) or DE 102 25 876.7 cited on page 4 of the specification by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck (4,186,183) by themselves or in combination as set forth above, further in combination with WO 88/09168.

The teachings of WO, DE, Caster, Poiani and Steck have been discussed above. What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids.

WO 88 teaches liposomal formulations containing doxorubicin for the treatment of tumors. The liposomes contain lecithin, phosphatidylglycerol, cholesterol and cryoprotectant. WO teaches that the liposomes can be dehydrated and reconstituted before use (Examples 1 and 2). WO 88 further teaches that the results indicate complete elimination of the gastrointestinal toxicity and alopecia (page 24, lines 1-17).

One of ordinary skill in the art would be motivated to use the liposomes of WO 82 containing lecithin, phosphatidylglycerol, cholesterol and a cryoprotectant in the generic teachings of WO 00 with a reasonable expectation of success since WO 82 teaches that the liposomes made from those components can be used for tumor treatment purposes and also such liposomes reduce the toxicity and side effects.

Applicant provides no specific arguments regarding this rejection.

5. Claims 34-43 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723) or DE 102 25 876.7 cited on

page 4 of the specification by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck (4,186,183) by themselves or in combination as set forth above, further in combination with Barenholz (6,156,337).

The teachings of WO, DE, Caster, Poiani and Steck have been discussed above. What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids.

Barenholz teaches liposomal formulations containing DMPG, phosphatidylcholine and cholesterol for the delivery of active substances and the advantages of using these phospholipids. The liposomal formulations contain a cryoprotectant and are dehydrated (col. 7, lines 15-28; col. 9, lines 19-57).

It would have been obvious to use the phospholipids taught by Barenholz in the generic liposomes taught by WO 00 because of the advantages taught by Barenholz.

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding WO, DE, Castor and Steck. Applicant argues that Barenholz only discloses liposomes comprising DMPC and DMPG in molar ratios of 9:1. This argument is not persuasive since Barenholz on col. 9 teaches the use of both DMPC and DMPG without giving any specific amounts and it is within the skill of the art to mix these two phospholipids in suitable appropriate amounts to obtain the best possible results.

6. Claim 28-49, 53-56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claims 28-37, 41-48 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723) or DE 102 25 876.7 cited on page 4 of the specification by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck (4,186,183) by themselves or in combination as set forth above: OR WO 00 04954 (English equivalent US 2003/0013723) or DE 102 25 876.7 cited on page 4 of the specification by themselves or in combination, further in view of Caster (5,776,486), Poiani (5,660,822), Steck (4,186,183) by themselves or in combination as set forth above, further in combination with WO 88/09168 also as set forth above, further in view of Ben-Hur, 6,010,890 or Kurono, 4,906,477.

The teachings of WO, DE, Caster, Poiani, Steck and WO 88 have been discussed above. What is lacking in these references is the teaching that the side effect is hemolysis.

The references of Ben-Hur and Kurono each teach that the administration of liposome results in the reduced hemolysis by the active agent (col. 6, lines 63-65 of Ben-Hur and col. 4, lines 10-13 of Kurono).

It would have been obvious to one of ordinary skill in the art that when the urokinase compounds of WO or DE are administered in liposomes, the hemolysis is reduced as taught by Kurono or Ben-Hur.

Applicant provides no specific arguments regarding this rejection.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK